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Divinylamines: Synthesis and Conversion into Azepine Derivatives

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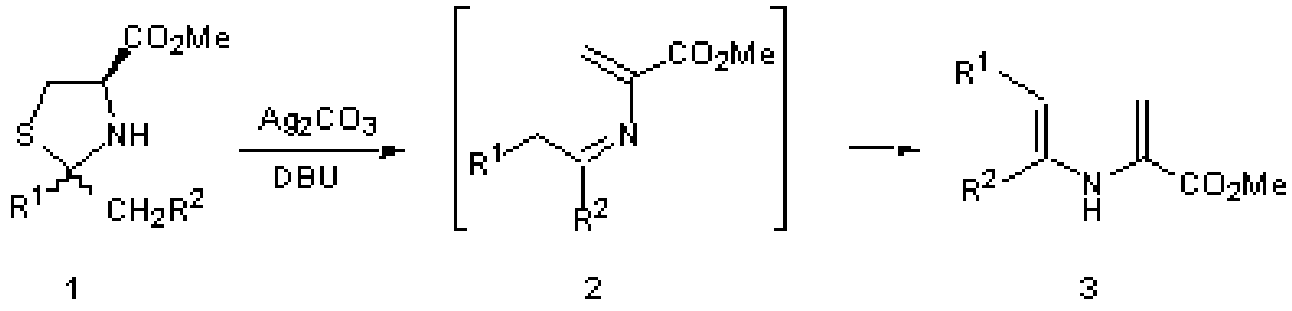
Abstract. Divinylamines (**3a - 3d**) were prepared by reaction of the corresponding thiazolidines (**1a - 1d**) with silver carbonate and DBU. The reaction of **3a** with DDQ led to the synthesis of an azepine derivative **7**.

Keywords: Divinylamines and azepine derivatives.

In a previous worh we reported that thiazolidines formed by reaction of cysteine methyl ester with a series of aldehydes react with silver carbonate and DBU leading to the formation of transients 1-substituted 2-azadiene-3-carboxylates.[1] The same synthetic methodology applied to thiazolidines (**1a - 1d**) formed by reaction of cysteine methyl ester with a-, b-oxoesters and 1,3-diketones generate 2-azadienes (**2a - 2d**) which tautomerize to isolable divinylamines (**3a - 3d**).[2]

Compound **3a** has also been prepared by the base catalysed reaction of methyl b-halo-a-aminopropionate hydrohalide[3] and this compound was used to generate pyrrole-2,3,4,5-tetracarboxylates[4a] and 7-azabicyclo[2.2.1]heptane-1,2,3,4-tetracarboxylates.[4b]

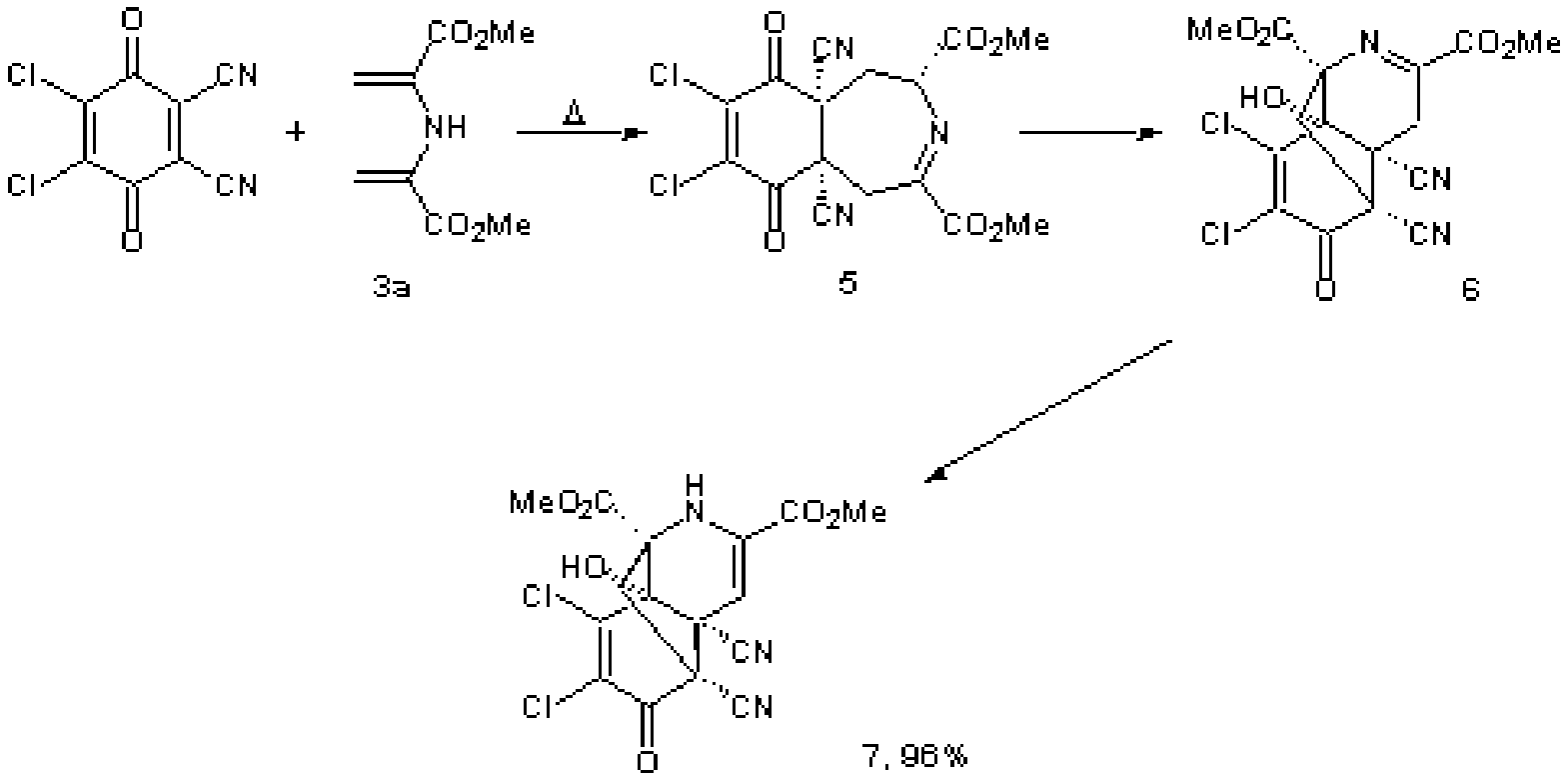
Our synthetic approach allows the synthesis of a range of divinylamine derivatives (Scheme 1). These compounds were produced from the corresponding 2-azadienes by prototropy and were stable for extended periods allowing the full chracterisation. The reaction is reversible and the azadienes can be trapped by promoting the Diels-Alder reaction with *N*-cyclohexen-1-ylpyrrolidine.[2] However the azadienes are not detected by nmr spectroscopy.



Scheme 1

The divinylamine derivatives obtained (**3a - 3d**) can be used as building blocks for heterocyclic synthesis. In fact compound **3a** and **3c** underwent a Hantszch type reaction when in presence of methyl vinyl ketone giving tetrahydropyridine**s**.[2]

In a attempt to convert **3a** into the corresponding pyrrol using DDQ as an oxidant a completely different reaction occurred. An azepine derivative **7** was formed in 96% yield (Scheme 2). The structure of this compound was established by X-ray crystallography[5] (figure 1).



Scheme 2

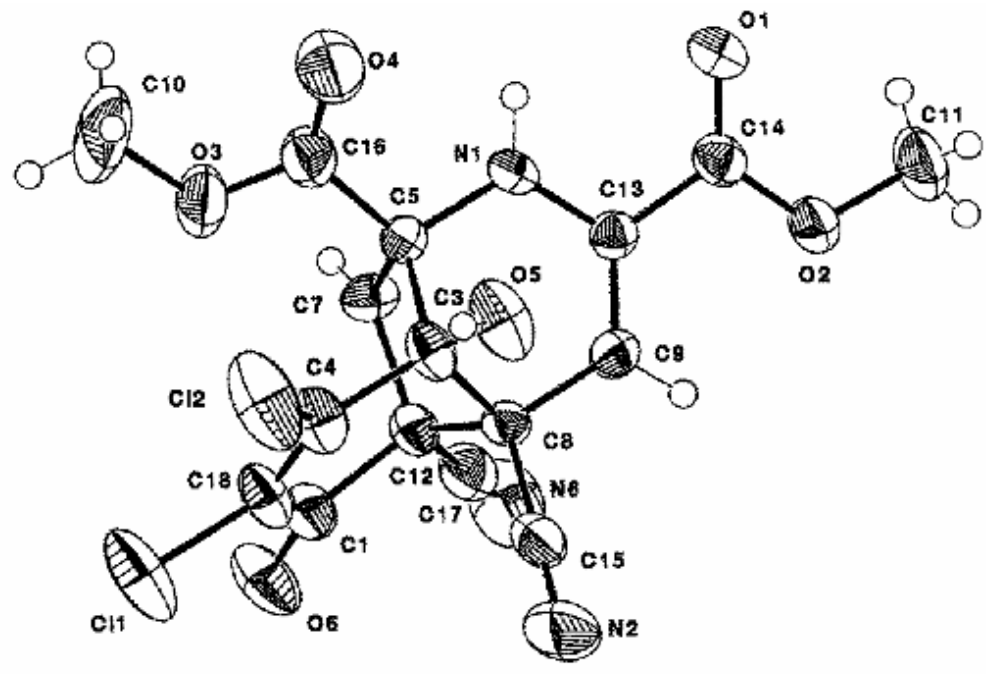
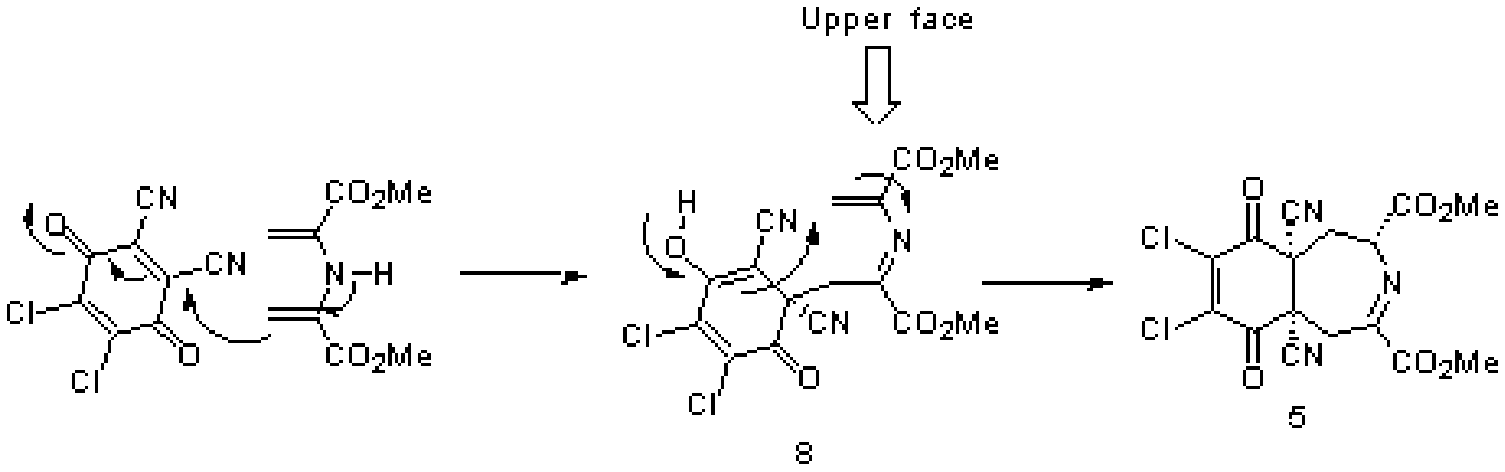


Figure 1 - X-ray crystal structure of compound **7**.[5]

The stereochemistry of the final product **7** allowed us to conclude that the reaction of divinylamine **3a** with DDQ involves the formation of the azepine derivative **5** as an intermediate.

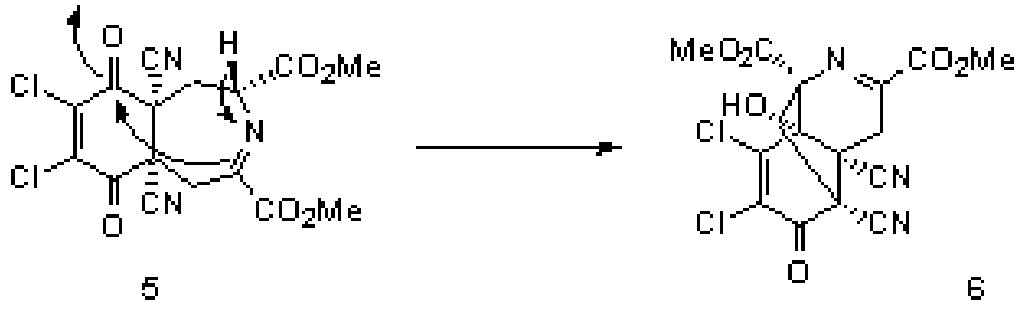
In the the Nenitzescu indole synthesis *p*-benzoquinones react with enamines to produce 5-hidroxyindole derivatives.[6] A conjugate addition occurs in which the enamine reacts at the terminal carbon followed by the cyclization to the indole. We suggest that, in a similar way, **3a** reacts with DDQ by a conjugate addition followed by the



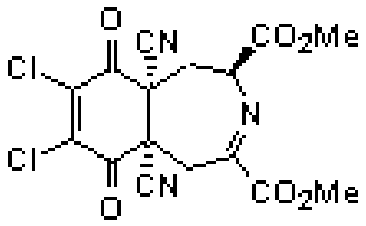
Scheme 3

cyclization to give compound **5**. The nucleophilic attack at the terminal carbon of the $CH_2=C(CO_2Me)N$ moiety of compound **8** will be from the lower face due to geometric restrictions making the addition of the proton from the upper face preferential. This mechanism imposes the stereochemistry of compound **5** (Scheme 3).

The tetrahydroazepine **5** underwent cyclization with the formation of compound **6** (Scheme 4). The geometry of compound **5** as given by molecular mechanics calculations[7-9] clearly points for the *exo*-trig cyclization to occur efficiently. Figure 2a shows the more stable conformation of compound **5** ($E = 1.225 \times 10^2$ kcal/mol) where the estimated distance between the reacting centers (C2-C6) is 4.129 Å and the distance between H attached to C4 and the O of the carbonyl group at C6 is 2.505 Å. On the other hand, the more stable conformation for compound **9** has less favorable geometry for the cyclization step (Figure 2b). The extremely high efficiency of the novel reaction can only be explained by the proposed stereochemistry for the intermediate **5**.



Scheme 4



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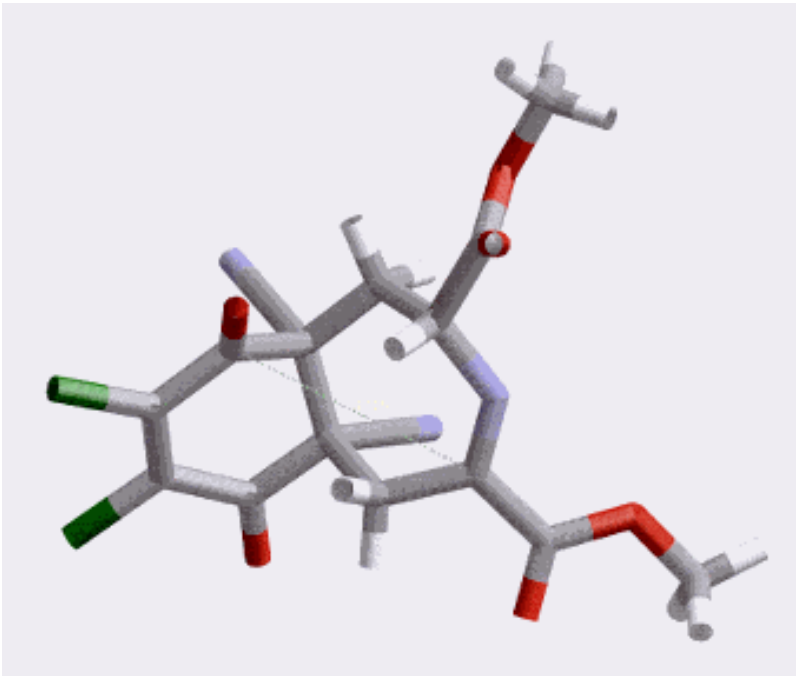
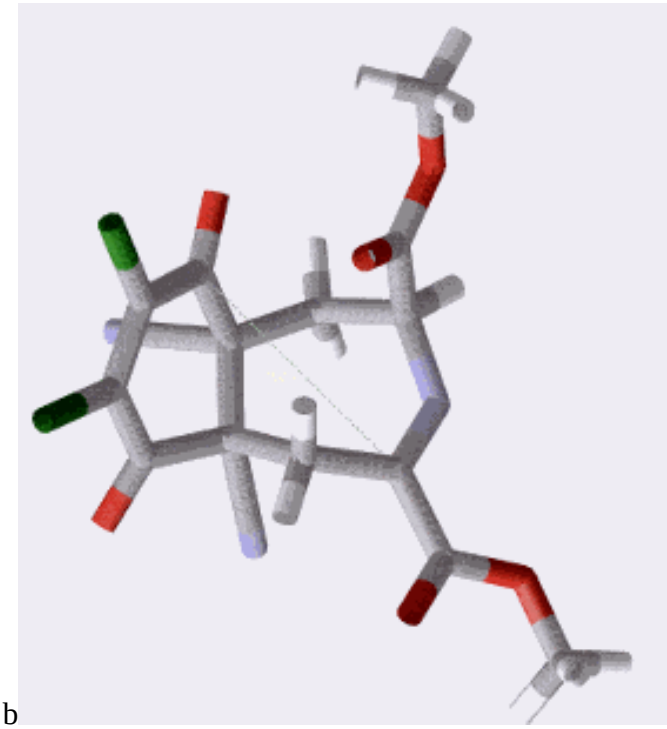
a.  b 

Figure 2 - a. compound **5**[7]; b. compound **9**.[7]

This type of reaction is currently being explored in order to obtain a general route to azepine derivatives.

Experimental Section

IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AMX300 spectrometer and on a Bruker ACE200 spectrometer. The solvent is deuteriochloroform except where indicated otherwise. Mass spectra were recorded on a VG Micromass 7070E instrument. M.p.'s were recorded on a Leitz Wetzlar 799 hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Thiazolidines **1a-1d** were prepared by the general procedure described in the literature.[1]

Preparation of divinyl amines derivatives. General procedure. The thiazolidine (1 mmol) was dissolved in dry acetonitrile (10 ml). The solution was cooled to −20 °C and silver carbonate (1 mmol) was added, followed by the addition of a solution of DBU (0.03 g) in dry acetonitrile (5 ml). The reaction mixture was stirred for 2 h at 0 °C then for 8 h at room temperature. Ether was added, the mixture was filtered and the solvent was evaporated from the filtrate. The products were isolated by flash chromatography.

2-Iminobis(propenoic acid) dimethyl ester (3a)

Methyl 2-methyl-2-(ethoxycarbonylmethyl)-thiazolidone-4-carboxylate **1a** gave, by the general procedure, followed by flash chromatography [petroleum ether-ethyl acetate (4:1) then petroleum ether-ethyl acetate (3:1)] 2-iminobis(propenoic acid) dimethyl ester **3a** as a solid (75%), m.p. 44-45 °C.

IR: n = 3370, 1724 and 1624 cm^{-1}.

^{1}H NMR (200 MHz): d = 3.85 (6 H), 5.06 (2 H, m) and 5.55 (2 H, m);

^{13}C NMR (50.3 MHz): d = 52.87, 97.26, 134.12, 165.05;

MS (EI+): *m/z* (%) = 185 [M+] (66), 153 (100), 94 (86), 66 (64), 57 (91) and 41 (88)

Anal.: Calc. for $C_8H_{11}NO_4$: 51.9; H, 5.9; N, 7.6; Found: C, 52.0; H, 6.1; N, 7.4%.

2-Iminobis(propenoic acid) ethyl methyl ester (3b)

Ethyl (2) methyl (4) 2-methylthiazolidone-2,4-dicarboxylate **1b** gave, by the general procedure, followed by flash chromatography [petroleum ether-ethyl acetate (4:1) then petroleum ether-ethyl acetate (3:1)] 2-iminobis(propenoic acid) ethyl methyl ester **3b** as an oil (51%) (at room temperature, solid with low melting point)

IR: n = 3372, 1724 and 1626 cm^{-1}.

^{1}H NMR (200 MHz): d = 1.35 (3 H, t), 3.85 (3 H), 4.30 (2 H, q) 5.03-5.05 (2 H, m), 5.53-5.54 (2 H, m) and 7.35 (1 H, NH);

^{13}C NMR (50.3 MHz): d = 14.061, 52.817, 61.992, 96.906, 97.094, 134.140, 134.341, 164.515, 165.032;

MS (EI+): *m/z* (%) = 199 [M+] (80), 167 (55), 153 (96), 94 (73), 66 (88), 55 (64) and 41 (100);

Anal.: Calc. for $C_9H_{13}NO_4$: C, 54.3; H, 6.5; N, 7.0; Found: C, 54.2; H, 6.6; N, 7.1%.

Methyl 2-[(1-methoxycarbonyl)vinylamino]but-2-enoate (3c)

Methyl 2-methyl-2-(ethoxycarbonylmethyl)thiazolidone-4-carboxylate **1c** gave, by the general procedure, followed by flash chromatography [petroleum ether-ethyl acetate (4:1) then petroleum ether-ethyl acetate (3:1)] methyl 2-[(1-methoxycarbonyl)vinylamino]but-2-enoate **3c** as an oil (50%) (at room temperature, solid with low melting point)

^{1}H NMR (200 MHz): d = 1.26 (3 H, t), 2.10 (3 H), 3.85 (3 H), 4.11 (2 H, q), 4.72 (1 H), 5.17 (1 H) and 5.71 (1 H).

Anal.: Calc. for $C_{10}H_{15}NO_4$: C, 56.3; H, 7.0; N, 6.6; Found: C, 56.4; H, 7.1; N, 6.5%.

Methyl 2-(1-methyl-3-oxo-but-1-enylamino)acrylate (3d)

Methyl 2-methyl-2-(acetylmethyl)thiazolidine-4-carboxylate **1d** gave, by the general procedure, followed by flash chromatography [petroleum ether-ethyl acetate (4:1) then petroleum ether-ethyl acetate (3:1)] Methyl 2-(1-methyl-3-oxo-but-1-enylamino)acrylate **3d** as an oil (71%) (at room temperature, solid with low melting point) .

^{1}H NMR (200 MHz): d = 2.09 (6H, s), 3.85 (3H, s), 5.21 (1H, s), 5.32 (1H, s) and 5.89 (1H, s);

^{13}C NMR (50.3 MHz): d = 20.01, 28.96, 52.56, 99.91, 110.06, 133.89, 157.44, 163.89 and 196.37;

MS (EI+): *m/z* (%) = 183 [M+] (22), 168 (4), 140 (40), 124 (14), 108 (41) and 43 (100).

Anal.: Calc. for $C_9H_{13}NO_3$: C, 59.0; H, 7.15; N, 7.65; Found: C, 59.06; H, 6.90; N, 7.39%.

Dimethyl 1,2,4a,5,6,8a-hexahydro-7,8-dichloro-4a,5-dicyano-8a-hidroxy-6-oxo-1,5-methyleneisoquinoline-1,3-dicarboxylate 7

A solution of the divinylamine **3a** (6.23 mmol) in toluene (40 ml) was stirred under nitrogen and DDQ (6.5 mmol) was added. The resulting mixture was heated under reflux for 2.5 hours. The product precipitated and was isolated by filtration as an yellow solid. Compound **7** was purified by crystallization (96%).

m.p. 209-211 °C (from ethyl ether-petroleum ether 40/60).

IR: n (KBr) = 1570, 1635, 1719 and 2256 cm^{-1}.

^{1}H NMR (200 MHz): d = 2.97 (1H, d, *J* 15, H-9a), 2.85 (1H, d, *J* 15, H-9b), 3.87 (3H, s, CO_2Me), 3.91 (3H, s, CO_2Me), 5.59 (1H, s, H-4) and 5.89 (1H, s, NH).

^{13}C NMR (50.3 MHz): d = 41.81, 53.40, 56.02, 63.35, 67.94, 77.84, 102.52, 113.22, 113.87, 130.12, 135.54, 154.72, 161.51, 166.11 and 178.27.

MS (FAB+): *m/z* (%) = 411 [M+(^{35}Cl)] (34).

Anal.: Calc. for $C_{16}H_{11}N_3O_6Cl_2$: C, 10.19; H, 2.69; N, 46.62; Found: C, 10.14; H, 2.70; N, 46.61%.

Acknowledgements

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